IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Andreas BERGMANN — Group Art Unit 1641

Serial No.: 10/551,298 — Examiner: Christine E. Foster

Filed: September 23, 2005 — Confirmation No.: 3226

For: DETERMINATION OF A MIDREGIONAL PROADRENOMEDULLIN PARTIAL PEPTIDE IN BIOLOGICAL FLUIDS FOR DIAGNOSTIC PURPOSES, AND IMMUNOASSAYS FOR CARRYING OUT SUCH A DETERMINATION

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Joachim Struck, declare as follows.

1. I am a co-inventor of the above-identified application and am the Director of Intellectual Property Development of BRAHMS Biomarkers, part of the Clinical Diagnostics Division of Thermo Fisher Scientific, Hennigsdorf, Germany. As a co-inventor, under German national law, I receive royalties for any commercial application of the invention claimed in the above-identified application.

2. The claimed method for determining the level in a sample of the mid-regional partial peptide of proadrenomedullin (mid-proAM) is unexpectedly advantageous in comparison to methods for determining the level of adrenomedullin (ADM) in a sample. This can be seen from a comparison of the known disadvantages of such ADM determinations which require special steps to resolve the resultant problems, versus the high reliability demonstrated for the claimed mid-proAM determinations. The advantages of the claimed determinations are due primarily to the unexpected stability of mid-proAM in plasma in contrast to the relative instability of ADM in plasma.

3. Known Problems in ADM Determinations

ADM determination problems have been summarized in Lewis et al., Clinical Chemistry, 44:3, 571-577 (1998). Lewis et al. state: "A number of assay systems for AM (adrenomedullin) have been published in brief, but in our laboratory, most extraction methods gave low and inconsistent results. We address the difficulties associated with measuring AM in human plasma and present the steps we took to resolve them." Page 571, col. 2, 1st paragraph. Lewis et al. observed that recovery of unlabeled ADM added to human plasma was only 56% ± 1.9%. They further observed that ADM immunoreactivity in plasma decreased by 20% after storage for only 24 hours at room temperature. They additionally reported that ADM can absorb unspecifically to surfaces, thereby additionally contributing to inaccuracy. See the Abstract, page 576, col. 2, second full paragraph, paragraph bridging pages 574 and 575, and page 576, col. 1, second and third full paragraphs. Furthermore, it is known that a binding protein for ADM circulates in plasma and that this binding can affect the accuracy of antibody-based determinations of ADM. (Popio et al., J. Biol. Chem., 2001; 276: 12292-300).

4. Unexpected Stability of Mid-proAM

In a literature report of the benefits of the claimed invention, the unexpected stability of mid-proAM is shown. Morgenthaler et al., Clinical Chemistry 51:10, 1823-1829 (2005). Based on my personal involvement and/or supervision of the experiments reported in Morgenthaler et al., I hereby attest to the truth and accuracy of the data and experiments reported therein. The Morgenthaler et al. publication is attached hereto and forms an integral part of this declaration.

Morgenthaler et al. also discusses the problems associated with ADM determinations in the prior art. See the first paragraph of the Abstract and also the first paragraph of the publication's text, both appearing on page 1823. The data reported in Morgenthaler et al. show that contrary to ADM, mid-pro AM (the term used in the claims of the above-identified application, which term refers to the same peptide named in Morgenthaler et al. "MR-proAMD.") is stable for at least three days

at room temperature and for at least fourteen days at 4 °C and one year at -20 °C. This greatly simplifies the taking of samples from patients and transporting of them to labs for reliable determinations. This alone represents a significant advantage in comparison to the instability of ADM and the resultant inaccuracies of ADM assays. As Lewis et al. concludes, "we suggest that considerable care is needed to ensure that accurate and reproducible results are obtained from studies quantifying this peptide [ADM]." (Last sentence of Abstract).

This significantly advantageous stability for mid-proAM in comparison to ADM results in a significant advantage for determinations of the former in comparison to the latter. For example, the level of care reported by Lewis is eliminated as a requirement. Nothing in the prior art or otherwise to my knowledge made this significant advantage predictable as of April 2003. It thus represents an unexpected, significant advantage for the determinations claimed in this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Joachim Struck

7.12.2010
Date:

AJZ/klb